

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 7/06	A1	(11) International Publication Number: WO 94/27563 (43) International Publication Date: 8 December 1994 (08.12.94)
<p>(21) International Application Number: PCT/US94/05361</p> <p>(22) International Filing Date: 16 May 1994 (16.05.94)</p> <p>(30) Priority Data: 068,256 28 May 1993 (28.05.93) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 068,256 (CON) Filed on 28 May 1993 (28.05.93)</p> <p>(71) Applicant (for all designated States except US): HANDEL- MAN, Joseph, H. [US/US]; 26 West 61st Street, New York, NY 10023 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): AHLUWALIA, Gurpreet, S. [US/US]; 8632 Stable View Court, Gaithersburg, MD 20879 (US). SHANDER, Douglas [US/US]; 16112 Howard Landing Drive, Gaithersburg, MD 20878 (US).</p> <p>(74) Agents: GALLOWAY, Peter, D. et al.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US).</p>		<p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: INHIBITION OF HAIR GROWTH</p> <p>(57) Abstract</p> <p>Mammalian hair growth is reduced by applying to the skin a composition including an inhibitor of 5-lipoxygenase.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

INHIBITION OF HAIR GROWTH

The invention relates to the inhibition of hair growth.

Arachidonic acid is released from
5 membrane lipids in response to injury or other
irritation. The enzyme 5-lipoxygenase converts
arachidonic acid into 5-hydroperoxycosa-
6,8,11,14-tetraenoic acid, which subsequently is
converted into a family of compounds known as
10 leukotrienes. The exact biological role of
leukotrienes has not yet been determined.

It has now been found that mammalian
(including human) hair growth can be inhibited
by applying to the skin a composition including
15 an inhibitor of 5-lipoxygenase in an amount
effective to reduce hair growth in the applied
area.

Examples of 5-lipoxygenase inhibitors
that have been found effective in reducing hair
20 growth include quercetin (3,3',4',5,7-
pentahydroxy flavone), dl- α -tocopherol, apigenin
(4',5,7-trihydroxy flavone), propyl gallate,
NDGA (nondihydroguaianetic acid), and caffeic
acid (3,4-dihydroxycinnamic acid). All of these
25 compounds are known in the art and are
commercially available. Other inhibitors of 5-
lipoxygenase are known in the art; see, for

- 2 -

example, Laughton et al., 42 Biochemical Pharmacology 1673 (1991).

5 The composition preferably includes a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread upon the skin. Examples of suitable vehicles are acetone, alcohols, or a cream, lotion, or gel which can effectively deliver the active compound. In addition, a penetration enhancer
10 may be added to the vehicle to further enhance the effectiveness of the formulation.

The concentration of the inhibitor in the composition may be varied over a wide range up to a saturated solution, preferably from 1 to
15 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the inhibitor
20 penetrates the skin. Generally, the effective amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be applied to the area of the body where it is desired to
25 inhibit hair growth. Typically, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition can also be applied to the legs, arms, torso or armpit.
30 The composition is particularly suitable for the treatment of hirsutism. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair
35 growth.

Reduction of hair growth is demonstrated when the frequency of hair removal

- 3 -

is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced. Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster.

To evaluate the effectiveness of a particular inhibitor, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 10-25 μ l. of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing the 5-lipoxygenase inhibitor is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The preferred 5-lipoxygenase inhibitors were tested according to the above procedure; the results are presented in Table 1. Vehicle A is acetone; vehicle B is 35% dipropylene glycol, 30% ethanol, 25% acetone, and 10% benzyl alcohol; vehicle C is 68%

- 4 -

purified water, 16% ethanol (200 proof), 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol, and 2% propylene carbonate; vehicle D is 80% ethanol (190 proof), 17.5%
5 purified water, 2% propylene glycol dipelargonate, and 0.5% propylene glycol; and vehicle E is a moisturizing lotion containing common cosmetic ingredients which include emulsifiers, detergents and preservatives.

Table 1

Compound	Dose	Vehicle	pH	HAIR MASS		Percent Inhibition
				Treated (mg)	Control (mg)	
Quercetin	5%	A	6.0	1.100±.10	1.543±.10	27±6
	10%	B	5.5	0.419±.07	2.679±.22	83±4
dl- α -Tocopherol	5%	A	5.0	0.400±.06	0.846±.10	49±7
Apigenin	5%	C	10.0	1.019±.22	2.230±.26	54±9
	10%	D	8.0	0.271±.0.09	1.380±0.22	82±5
Propyl gallate	5%	D	7.0	0.870±.15	2.553±.16	67±5
NDGA	10%	D	6.5	0.450±.11	2.391±.21	81±4
Caffeic acid	5%	D	6.0	1.740±.06	2.424±.17	26±5
	15%	E	4.0	0.797±.13	2.148±.22	62±7

- 6 -

It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without
5 departing from the spirit or scope of the invention or of any embodiment thereof.

- 7 -

C L A I M S

1. A process of inhibiting mammalian hair growth, comprising applying to the skin a composition including an inhibitor of 5-lipoxygenase in an amount effective to reduce hair growth.
2. The process of claim 1, wherein said inhibitor is quercetin.
3. The process of claim 1, wherein said inhibitor is dl- α -tocopherol.
4. The process of claim 1, wherein said inhibitor is apigenin.
5. The process of claim 1, wherein said inhibitor is propyl gallate.
6. The process of claim 1, wherein said inhibitor is NDGA.
7. The process of claim 1, wherein said inhibitor is caffeic acid.
8. The process of claim 1, wherein said concentration of said inhibitor in said composition is between 1% and 30%.
9. The process of claim 1, wherein the composition is applied to the skin in an amount of from 100 to 3000 micrograms of said inhibitor per square centimeter of skin.
10. The process of claim 1, wherein the composition is applied to the skin on the face of said mammal.
11. A method of producing a composition for inhibiting mammalian hair growth, which comprises selecting an inhibitor of 5-lipoxygenase, and combining said inhibitor, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.
12. A method according to claim 11, wherein said vehicle or carrier is adapted to be

- 8 -

spread upon the skin of a mammal.

13. A method according to claim 11,
wherein said inhibitor is as defined in any one
of claims 2 to 8.

5 14. The new use of an inhibitor of 5-
lipooxygenase for reducing hair growth.

15. A composition when used for inhibiting
mammalian hair growth, which includes an
inhibitor of 5-lipooxygenase in an amount
10 effective to reduce hair growth and a non-toxic,
dermatologically acceptable vehicle or carrier.

16. A composition according to claim 15,
wherein said inhibitor is as defined in any one
of claims 2 to 8.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 13, no. 308 (C-617) & JP,A,01 196 126 (KAO CORP.) 14 April 1989 see abstract ---	1,2,8-16
A	US,A,4 530 844 (EMERBECK ET AL.) 23 July 1985 see the whole document ---	1-3,6, 8-16
A	DATABASE WPI Week 8441, Derwent Publications Ltd., London, GB; AN 84-254475 & JP,A,59 155 314 (RIKAGAKU KENKYUSHO) 4 September 1984 see abstract ---	1,7-16
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

29 September 1994

Date of mailing of the international search report

10.10.94

Name and mailing address of the ISA

European Patent Office, P.B. 3818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Fischer, J.P.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S.T.N., File Supplier, Karlsruhe, DE, File Chemical Abstracts, vol 101, n 2087 see the abstract -----	1,5,8-16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/05361

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1, 8-16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The inhibition of 5-lipoxygenase is a property of many compounds. Due to the broadness of claim 1, the search has been carried out and based on the examples.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4530844	23-07-85	CA-A- 1240931 US-A- 4568696	23-08-88 04-02-86
